achieved when the coronary artery was reopened later than four hours after occulsion, which is indicated by the onset of pain. Myocardial salvage was assessed by thallium 201 scintigraphy done before and after recanalization. Significant myocardial salvage resulted in a delayed improvement of abnormal regional wall motion and rises in left and right ventricular ejection fractions days and weeks after reperfusion. There is suggestive evidence that successful early reperfusion results in significantly reduced mortality. Hematomas at the site of punctures and arrhythmias, usually not serious, are fairly frequently occurring complications of intracoronary thrombolysis. In recent studies in which streptokinase was administered in large doses intravenously rather than intracoronarily, results were similar to those of the intracoronary route. Large controlled studies will be necessary to definitely assess the effect of thrombolysis on mortality, to identify subsets of patients who can benefit most from the procedure and to define time limits of effective intervention in various patients.

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Chemotherapy for Disseminated Germ Cell Cancer

GERM CELL TUMORS arise from the testes and ovary as well as extragonadal sites. Whereas localized germinal neoplasms are curable by surgical treatment or radiotherapy, or both, disseminated tumors such as advanced testicular cancer have historically been difficult to eradicate. Since the mid 1970s, new drugs such as bleomycin and cisplatin have been used in combination chemotherapy programs for patients who have advanced testis cancer. The three-drug combination of vinblastine, bleomycin and cisplatin has been used by Einhorn and co-workers with dramatic results. In an initial series of 47 patients who had advanced testis cancer, 33 (70 percent) achieved complete disease regression using four cycles of the three-drug combination administered over a 12-week induction therapy period. Similar regression rates have been achieved in subsequent series. Complete response correlated with the bulk of the initial tumor—large tumor masses being unfavorable for achieving complete regression—but all histologic subtypes of germ cell tumors responded.

In 4.5 to 6.5 years of follow-up, 6 out of 33 originally complete responders have relapsed. Most relapses occurred in the first year, none after two years. Patients in continuous complete remission at two years are considered cured. During the initial development of "Einhorn" chemotherapy, maintenance chemotherapy was administered for two years. Recent studies have shown no benefit from this type of prolonged maintenance treatment. Among large series of testis cancer patients achieving complete remission with combination chemotherapy, the relapse rate even without maintenance treatment may be as low as 10 percent or less.

Germ cell neoplasms are diseases of young people. New chemotherapy combinations have markedly increased the curability of germ cell tumors of the testes and appear to be very beneficial in the treatment of ovarian germinal neoplasms and extragonadal germ tumors as well.

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Hepatitis B Vaccine

A VACCINE (Heptavax-B, Merck, Sharp and Dohme Research Laboratories) has been introduced that offers the potential of eliminating viral hepatitis, type B. The disabling effects of acute type B hepatitis, combined with the long-term features of chronic viral infection that include the possible development of hepatoma, make this an extremely important breakthrough. Considerations of cost, availability and safety, however, combined with a population at relatively low risk, have already produced controversy about whom to vaccinate.

The development of this vaccine has taken advantage of two characteristics of the hepatitis B virus: the chronic carrier state and the overproduction by the carrier of coat protein (hepatitis B surface antigen). The antigenic particle is much smaller than the virus itself and is separated by ultracentrifugation. Further steps including formalin inactivation lead to a highly purified, theoretically safe product. Because we are unable to grow this virus in culture, plasma from chronic carriers is used. Future research or the use of modalities such as recombinant techniques may of course change this approach.

The antigen in this vaccine achieves its purpose. In more than 90 percent of recipients in studies to date, antibody titers develop. That this antibody is protective has been shown in studies with homosexual men who have an extraordinary attack rate that is nearly eliminated in vaccine responders. Whether or not this protection is retained for a long time, as expected, will need to be shown.

Safety is an issue that cannot be adequately addressed at this time. No major side effects have been reported to date in trials totaling 25,000 to 50,000 doses of vaccine. What will happen when this number reaches the millions is pure conjecture. All of the various concerns about vaccines have been voiced. But an extremely careful development and testing program has provided as much information as we can expect at this time.

Based on efficacy, presumed safety and cost (about $100 per treatment) what can we recommend? Clearly those at greatly increased risk such as promiscuous homosexual men (80 percent risk) and sexual partners of carriers (50 percent risk) need attention. Health care workers in direct contact with blood, either in patient care (dialysis workers, special unit nurses and the like) or ancillary services (such as phlebotomists and clinical laboratory technicians) have a variable

exposure with an estimated risk of 2 percent to 3 percent a year. In the view of most experts, this amount of risk justifies immunization.

The manufacturer recommends antibody testing (hepatitis B surface antibody at $20 per test) before vaccination to eliminate unnecessary and costly injections in people who have naturally acquired immunity. While this is the current standard, its cost effectiveness has been questioned. Clearly the response rate to the vaccine eliminates the need for follow-up antibody studies in all but special circumstances.

What is needed is a low-cost safe method for attacking this global problem. We now have what appears to be a very good beginning.

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Plasmapheresis as Therapy

PLASMAPHERESIS, or plasma exchange, a new and sophisticated form of bloodletting, is rapidly becoming a major therapeutic tool for the treatment of a variety of disease processes. This innovation has been made possible by technologic advances in centrifugation that allow the separation of various cell components from plasma of human blood. About 41,000 such apheresis procedures were done in the United States last year on a minimum of 41 different disease processes. The data base for the entire industry is based on anecdotal reports. Only now are double-blind studies being done to further delineate the indications and to compare the efficacy of this form of treatment with other conservative measures. The one group of diseases wherein the use of plasmapheresis seems to be clearly accepted by all is the hyperviscosity syndromes in which aberrations in blood flow occur as a result of the presence of abnormal blood proteins. Here the procedure is of most value in an acute crisis. Long-term management requires both plasmapheresis and immunosuppressive therapy.

Despite the limited data base, recognized authorities in the field suggest that there is enough information available to justify plasmapheresis in certain clinical settings. In most cases it is assumed that immunologic mediators of disease are removed in the process of plasmapheresis. Besides the hyperviscosity syndromes, plasmapheresis may also be beneficial for the following disorders:

- Myasthenia gravis, especially in patients who have failed to respond to steroids and antimetabolite therapy or in those who are in an acute respiratory crisis.
- Goodpasture's syndrome, biopsy proved or associated with lung hemorrhage, and acute crescentic nephritis that is rapidly progressing and not responding to steroid drugs.
- Lupus nephritis, the classic circulating immune complex disorder. Unfortunately, the criteria for the use of plasmapheresis have not yet evolved in this disorder and double-blind studies are only now under way to exactly define its value.
- Rapidly progressing systemic sclerosis with not only skin but also multiorgan system involvement, though the number of cases so far is extremely small and widespread clinical use probably cannot be justified and should be restricted to academic centers. The same holds true for other rheumatic diseases such as polymyositis and dermatomyositis.

Plasmapheresis is a popular and rapidly expanding area in which only time and additional studies are needed to give this tool its proper place in clinical practice. English physicians have recently suggested that all patients who receive an apheresis procedure should be in a clinical registry so that a maximum amount of information can be obtained regarding this treatment. This should also be done in this country.

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Calcium Channel Blocking Agents in Cardiovascular Medicine

THE CALCIUM CHANNEL blocking agents are a heterogeneous group of compounds that represent a new generation of drugs for the treatment of cardiovascular disease. Their therapeutic actions derive from their capacity to inhibit calcium flux through the "slow" channels of cardiac and smooth muscle cell membranes. The slow channels are so named because cellular entry of calcium is normally delayed during electrical depolarization until the plateau phase of the action potential, in contrast to sodium transmembrane passage through the "fast" channels at the initiation of depolarization. The electrical and contractile functions of cardiac and smooth muscle tissue are dependent on this phasic cellular entry of calcium which activates calcium-dependent adenosine triphosphatase (ATPase), an essential step in excitation-contraction coupling. Skeletal muscle cells, however, have abundant intracellular calcium stores and their activity does not depend on influx of calcium. Therefore, agents that inhibit calcium flux can modulate cardiac and smooth muscle activity, an effect with therapeutic potential in certain conditions.

The cardiovascular effects of the calcium antagonists are the result of their direct and indirect actions on the heart and vasculature at multiple levels. The direct effects of inhibition of calcium transport by these agents are smooth muscle relaxation and thus systemic and coronary vasodilation and negative cardiac inotropy. Depending on the specific drug, these agents either have